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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,458	AVITAL ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- Th MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-42 are pending and under current examination.

Election/Restrictions

Applicant's election with traverse of the species proteins expressed by genes that encode the MHC in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the restriction requirement is improper. In particular, Applicants argue that the various species of markers recited in the claims can be associated with cells that are not stem cells, but the identification of stem cells by the methods of the present invention is not accomplished simply by searching for cells that express one of the aforementioned markers. Applicants argue that the cells are first sorted based upon β_2m expression. [See p. 3, 1st ¶ of the Response].

Applicants' arguments are found persuasive, and the Restriction requirement mailed 9/19/02, Paper No. 6, is withdrawn and all claims are under current examination.

Drawings

The drawings are objected to for reasons advanced on the Notice of Draftsperson's Patent Drawing Review [Form PTO-948]. A proposed drawing correction or corrected drawings are required in reply to the Office action to

avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Applicant(s) is/are hereby notified that the required timing for correction of drawings has changed. See the last 6 lines on the sheet, which is attached, entitled "Attachment for PTO-948 (Rev. 03/01 or earlier)". Due to the above notification Applicant(s) is/are required to submit drawing corrections with the time period set for responding to this Office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of isolating stem cells comprising obtaining a sample of cells from a mammal, sorting cells that express β_2m from cells that do not express β_2m, and sorting from the population of cells that do not express β_2m cells which express a particular stem cell marker, does not reasonably provide enablement for methods for

isolating stem cells of a mammal comprising obtaining a sample of cells, sorting cells that express β_2m from cells that do not express β_2m. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to methods of isolation of stem cells of a mammal comprising obtaining a sample of cells from the mammal, sorting, from the sample, cells that express β_2-microglobulin [β_2m] from cells that do not express β_2m; selecting stem cells from the sample of cells that do not express β_2m. In further embodiments, the methods are directed to further selecting the stem cells by specific stem cell markers [e.g., proteins expressed by one or more genes encoding the major histocompatibility complex, Thy-1, RT1A, etc.].

The specification teaches many stem cells, including liver, spleen and neuronal stem cells, do not express β_2m, and that β_2m is a highly conserved immune molecule and appears on all that cells that have a nucleus. The specification teaches that only a few cells, such as spermatozoa and certain cells at the inner cell mass membrane of the embryo are known to lack β_2m. [See p. 6, lines 1-10]. The specification teaches that stem cells can be sorted from a sample of cells by first sorting by β_2m expression [or lack thereof] and that the β_2m- sample can be sorted by stem cell-specific markers. The specification teaches various markers that can be used to identify liver and

neuronal stem cells [see Table 1]. In particular, the specification teaches the isolation of hepatocytes from human and rat liver [see Example 1]. Human tissue specimens and rat specimens were obtained and quantitative analysis was done on various specimens to analyze expression of MHC, hematopoietic and liver associated markers. It was found that a particular blast-like cell was present in all source material. These cells, in contrast to all other nucleated cells, did not express β_2m. In normal rat livers, these cells were occasionally seen in normal rat livers in small amounts, whereas they were numerous in diseased rat livers. These β_2m$^-$ cells were tested to identify various hematopoietic stem cell markers expression(s). It was found that approximately 99% of the β_2m$^-$ cells expressed Thy-1 and are committed hepatocyte progenitors.

The specification further teaches that β_2m$^-$ cells were isolated from the bone marrow of rats. From this population of cells, five different subpopulations were selected [CD34$^+$, c-Kit$^+$, flt-3$^+$, Thy-1$^-$ and Thy-1$^+$] and stained the subpopulations for ALB. It was found that only the Thy-1$^+$ cells had a complete positive albumin signal. As such, it was concluded that the β_2m$^-$/Thy-1+ fraction represented bone marrow-derived hepatocyte stem cells [see Example 2]. The specification further teaches that neural stem cells were isolated from human fetal brain, and approximately 100,000 cells were taken as neurospheres to be sorted by FACS. Antibodies to β_2m were added to the suspension, as well as HLA class II. Cells were sorted by FACS and

differentiated by plating onto glass slides. It was found that Class I and β_2m expression was low and heterogeneous on the cell surface of neuronal progenitor cells, whereas post-differentiation, class I expression decreased, and β_2m expression was high and homogeneous in more differentiated cells. [See Example III].

The claims, as broadly written, are not enabling because as stated by the specification [p. 6, lines 1-10], cells such as spermatozoa do not express β_2m. As such, in obtaining a sample of cells [see line 3 of claim 1, for example] and sorting β_2m- cells from β_2m+ cells and further selecting stem cells from the β_2m- cell population, would not necessarily result in the isolation of stem cells, as the "sample of cells", as broadly claimed, could contain other cells that would not be stem cells, for example, spermatozoa.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to isolating a population of stem cells by merely sorting β_2m- cells, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20, 27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as written, is incomplete. The claim recites "selecting stem cells from a sample of cells" in lines 6-7 of the claim. It is unclear how the stem cells are "selected" from a sample of cells, as the metes and bounds of the term "selected" are not specifically defined. Although further claims limit the term "selected", claim 1 is missing critical steps because it is not clear how merely selecting cells would result in isolating stem cells. Claims 2-20 depend from claim 1.

Claim 6, as written, is unclear. The claim recites a further step of isolating pluripotent stem cells, however, the claim does not provide specific steps in order to show that such selection would result in pluripotent stem cells, for example, what selection criteria would be used?

Claim 7, as written, is unclear. The claim recites a step of further selecting embryonal stem cells, however, the claim does not provide specific steps to show that selection would result in embryonal stem cells. For example, what selection criteria would be used to select such cells?

Claims 10 and 27, as written, are unclear. The claim recites that the MHC marker of claim 8 or claim 25, respectively, is Thy-1. This is unclear because Thy-1 is not a MHC antigen [see Roitt *et al.* **Immunology**, p. 4.10-4.11, Figure 4.23 and p. 4.11, 2nd column 1st ¶].

Claims 11 and 29, as written, are unclear. The claim recites that the MHC marker of claim 8 or 25, respectively, is a marker consisting of flt-3, CD34, c-kit, CD38. This is unclear because these markers are not MHC markers.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsukamoto *et al.* [US Pat. No. 5,643,74, published July 1, 1997, cited on Applicants' Information Disclosure Citation filed April 8, 2002, Paper No. 4].

The claims are directed to isolated stem cells that do not express β_2m, express Thy-1, is derived from the bone marrow or liver of a mammal, is a pluripotent or embryonic stem cell.

The properties of the claimed stem cells are inherent properties of the stem cells. It is noted that, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its

properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Tsukamoto teach the identification and isolation of human hematopoietic stem cells. In particular, they teach that Thy-1 is a molecule that has been identified in rat and mouse hematopoietic stem cells [see col. 1, lines 65-67]. They further teach that the hematopoietic stem cells are pluripotent [see col. 6, lines 30-50] and that the cells were isolated from human fetal bone marrow, human fetal livers, and adult bone marrow [col. 9, lines 13-30].

Accordingly, Tsukamoto anticipate the claimed invention.

Claims 37, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson *et al.* [**Science** 1998, 282:1145-1147].

The claims are directed to an isolated stem cell that does not express β_2m, is pluripotent, and is an embryonic stem cell. Note that the lack of expression of β_2m is an inherent quality of stem cells, see *supra*.

Thomson teach pluripotent human embryonic stem cell lines which were derived from human blastocysts [see *Abstract*].

Accordingly, Thomson anticipates the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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